Prognostic Significance of Coronary Collaterals in Patients With Coronary Heart Disease Having Percutaneous Transluminal Coronary Angioplasty

Jeroen Koerselman, MD, PhD[a], Peter P.T. de Jaegere, MD, PhD[c], Marianne C. Verhaar, MD, PhD[b], Diederick E. Grobbee, MD, PhD[a], and Yolanda van Der Graaf, MD, PhD[a,*], for the SMART Study Group[†]

We examined the presence and extent of coronary collaterals as a prognostic determinant of cardiovascular outcome in a prospective case-cohort study of 655 patients admitted for elective coronary angioplasty. In patients with ischemic heart disease, the angiographic presence of coronary collaterals may mark an unfavorable prognosis, particularly in relatively high-risk patients. **(Am J Cardiol 2005;96:390–394)**

From a pathophysiologic point of view, a direct and positive relation between coronary collaterals and a better outcome is to be expected. However, the presence of collaterals is related to, among others, the duration and extent of ischemic disease and is thus a marker of its severity.[1–3] Therefore, it is not yet clear whether the presence of coronary collaterals in unselected patients with ischemic heart disease reflects the severity of coronary artery disease and thus a worse prognosis in the long term, or whether its presence helps to prevent a future occurrence of cardiovascular events by protecting against ischemia. In the present study, we examined the presence and extent of coronary collaterals as a long-term prognostic determinant of cardiovascular outcome in an unselected group of patients referred for elective coronary angioplasty. In addition, patients were stratified according to cardiac risk (estimated using the Framingham coronary heart disease [CHD] risk score[4]) to examine whether the prognostic significance of coronary collaterals varies by disease severity.

• • •

The institutional review board of the University Medical Center Utrecht (UMC Utrecht) approved this study. All patients provided written informed consent. The procedures followed were in accordance with our institutional guidelines.

A prospective case-cohort study was separately performed within the Second Manifestations of ARTerial disease (SMART) study. The SMART study is an ongoing prospective cohort study conducted at the UMC Utrecht.[5] At enrollment, the patient's medical history is recorded with a standardized questionnaire, and height, weight, and blood pressure are measured. Blood and urine samples are taken. Information on the occurrence of new fatal or nonfatal cardiovascular disease and cardiovascular interventions during follow-up is obtained by contacting the patients every 6 months. Follow-up for the present study ended March 1, 2003. For the present study, we used a case-cohort design.[6] The study population consisted of all 655 patients who were admitted for elective percutaneous transluminal coronary angioplasty (PTCA) and took part in the SMART study between January 1, 1998 and July 8, 2002. For the control group, a 20% random sample of 131 of the 655 patients (20%) was selected. Cases consisted of all patients in whom a cardiovascular event occurred during follow-up, a total of 152 patients, 25 of whom had also been selected in the random sample.

The baseline angiographic data for 258 patients who underwent PTCA were retrieved (131 + 152 − 25 = 258). Baseline diagnostic coronary angiograms could not be retrieved for 14 patients (3 from the control group and 11 cases); subsequently, these patients were excluded from the study. Therefore, baseline coronary angiograms were reviewed for 244 patients who underwent PTCA (258 − 14 = 244). The presence and extent of coronary collaterals on each baseline coronary angiogram were defined and visually assessed using Rentrop's classification (grade 0, no filling of collateral vessels; grade 1, filling of collateral vessels without any epicardial filling of the recipient artery; grade 2, partial epicardial filling by collateral vessels of the recipient artery; and grade 3, complete epicardial filling by collateral vessels of the recipient artery).[7] The coronary collateral presence was defined as the presence of minimal or well-developed collaterals (Rentrop grade 1, 2, or 3).[8,9] Grading was done independently by a trained research physician

[a]Julius Center for Health Sciences and Primary Care and [b]Department of Vascular Medicine, University Medical Center Utrecht, Utrecht; and [c]Department of Cardiology, Erasmus Medical Center, Rotterdam, The Netherlands. Manuscript received December 9, 2004; revised manuscript received and accepted March 21, 2005.

This study was supported by the Netherlands Organisation for Health Research and Development (ZonMw, project 904-65-095), The Hague, The Netherlands, which had no involvement in the writing of this paper or its submission. Dr. Verhaar was supported by the Netherlands Organisation for Scientific Research (grant 016-036-041), The Hague, The Netherlands.

* Corresponding author. Tel. 31-30-250-9351; fax: 31-30-250-5485.

E-mail address: Y.Vandergraaf@jc.azu.nl (Y. van Der Graaf).

[†] The list of study investigators can be found in the Appendix.

0002-9149/05/$ – see front matter
doi:10.1016/j.amjcard.2005.03.083

(JK) and cardiologist (PPTdJ), who were unaware of the clinical data. If an angiogram was graded differently, a consensus was obtained. The pre-PTCA angiograms were graded in random order. To assess the interobserver variability of the grading, 100 randomly selected coronary angiograms were scored by another cardiologist, who was not involved in the study and was unaware of the results of the reading of the 2 other observers and of the clinical data, during a separate session. The strength of agreement between the 2 observers (JK and PPTdJ) and the other cardiologist was good (κ 0.65, 95% confidence interval [CI] 0.51 to 0.79). The reproducibility of Rentrop's score was described previously as very good (κ 0.85, 95% CI 0.77 to 0.93).[10]

In the present study, we considered the presence of coronary collaterals as a measure of a patient to form collaterals in vascular areas other than the heart, such as the brain and peripheral circulation. Therefore, we defined the cardiovascular outcome as a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, any cardiovascular intervention, or any amputation of lower extremities. The outcome of interest was defined as the first cardiovascular event occurring during follow-up. In case potential outcomes of interest occurred, additional information was collected from either the patients' specialist or general practitioner.

Cardiovascular death was defined as fatal cerebral infarction, fatal myocardial infarction, sudden death, or fatal rupture of an abdominal aortic aneurysm. Nonfatal myocardial infarction was defined by the presence of $\geq$2 of the 3 following characteristics: (1) ischemic chest pain of $\geq$30 minutes' duration, (2) an increase in the MB-fraction of creatine kinase to more than twice the upper level of normal, and (3) characteristic changes on the electrocardiogram consistent with the diagnosis. Nonfatal stroke was defined as a focal brain injury persisting for $>$24 hours, combined with an increase in handicap of $\geq$1 point on the Rankin scale. A distinction was made between a cerebral infarction and a cerebral hemorrhage, on the basis of computed tomography or magnetic resonance imaging, if available. Cardiovascular intervention was defined as any coronary artery bypass graft, PTCA, carotid endarterectomy, or revascularization (surgical or using percutaneous transluminal angioplasty) of the aorta or 1 of its branches or of the iliac, femoral, or crural arteries. An amputation of the lower extremities was defined as any amputation (or part) of a toe, foot, or leg because of chronic ischemia.[5] All events were reviewed by 3 members of an independent clinical event committee for final diagnosis and classification and coded as previously described.[5] If an event was classified differently, a consensus was obtained.

Unless otherwise specified, the data are presented as the number with the percentage or the mean $\pm$ SD. First, the association between the presence and absence of coronary collaterals and cardiovascular outcome was quantified using the unweighted Cox proportional hazards model by Prentice,[6] which is particularly suitable for analyzing case-cohort data. This weighting method is incorporated into a Statistical Analysis Systems macro written by Barlow et al,[11] and made available through Statlib on the Internet (http://lib.stat.cmu.edu/general/robphreg).[11] Subsequently, the analyses were repeated with adjustment for variables known to potentially affect the association examined, notably male gender, age, a history of myocardial infarction, a history of PTCA or coronary artery bypass grafting, and multivessel coronary disease.

Second, the relation between the extent of coronary collateral circulation (Rentrop grades 1, 2, 3, vs 0 taken as the reference category) and cardiovascular outcome was quantified with the unweighted Cox proportional hazards model by Prentice,[6] both unadjusted and with adjustment for the variables previously mentioned. Finally, to examine whether the prognostic significance of coronary collaterals varied by disease severity (the amount of cardiovascular disease already present), the analyses were repeated with the patients stratified according to cardiac risk, estimated using the Framingham CHD risk score.[4] Patients were classified as relatively low or high risk according to the median estimated risk score.

Hazard ratios with robust 95% CIs are presented. A 2-sided p value $<$0.05 was considered statistically significant. We used the statistical package Statistical Analysis Systems for Windows, release 8.02 (SAS Institute, Cary, North Carolina).

The baseline and clinical characteristics of the 244 patients studied are presented in Table 1. Coronary collaterals were present in 91 patients (37%); 13 patients had grade 1 (no epicardial filling), 33 had grade 2 (partial epicardial filling), and 45 had grade 3 collaterals (complete epicardial filling). The median estimated Framingham CHD risk score was 13% (range 1% to 53%). Therefore, patients with a CHD risk score $<$13% were classified as relatively low risk and those with a risk score $\geq$13% were classified as relatively high risk.

The median follow-up time was 2.6 years (range 0.2 to 4.6). A first cardiovascular event occurred in 141 patients. Three patients died of cardiovascular disease: sudden death occurred in 2 patients and 1 patient died of congestive heart failure. A nonfatal myocardial infarction occurred in 26 patients and a nonfatal ischemic stroke in 4 patients; a cardiovascular intervention was necessary in 108 patients (Table 2).

Table 3 lists the results of the analyses regarding the presence and extent of coronary collateral circulation and the risk of a first cardiovascular event, both unadjusted and adjusted for male gender, age, a history of myocardial infarction, previous coronary intervention, and multivessel coronary disease. Overall, the presence of coronary collaterals at baseline tended to indicate a greater risk of subsequent cardiovascular events. This adverse effect was most pronounced in patients with a relatively high CHD risk (hazard ratio [HR] 2.22, 95% CI 1.08 to 4.55), but was less

Table 1
Baseline and clinical characteristics of study population

Characteristic	All Patients Studied (n = 244)	Cases (n = 141)	Control Group (n = 103)	p Value
Age at index PTCA (yrs) (mean ± SD)	58.1 ± 9.2	58.5 ± 9.1	57.5 ± 9.4	0.40
Male gender	203 (83%)	121 (86%)	82 (80%)	0.20
Current smoker	69 (29%)	38 (27%)	31 (30%)	0.64
Current alcohol consumption	186 (77%)	105 (76%)	81 (79%)	0.57
Diabetes mellitus	49 (20%)	34 (24%)	15 (15%)	0.07
Hypertension	91 (38%)	54 (40%)	37 (36%)	0.59
Hyperlipidemia*	203 (84%)	121 (86%)	82 (80%)	0.16
BMI ≥30 kg/m^2	43 (18%)	28 (20%)	15 (15%)	0.28
Framingham CHD risk†				
CHD risk (%) (Mean ± SD)	15.4 ± 9.9	16.3 ± 10.6	14.2 ± 8.8	0.12
Low CHD risk (<13%)‡	109 (46%)	59 (44%)	50 (50%)	‡
High CHD risk (≥13%)	126 (54%)	75 (56%)	51 (51%)	0.41
Previous AP	224 (92%)	132 (94%)	92 (89%)	0.15
On exertion	171 (72%)	103 (76%)	68 (66%)	0.10
During emotion	77 (32%)	45 (33%)	32 (31%)	0.78
Previous TIA or stroke	24 (10%)	9 (6%)	15 (15%)	0.04
Previous MI	106 (44%)	71 (51%)	35 (34%)	<0.01
Previous PTCA or CABG	77 (32%)	51 (36%)	26 (25%)	0.07
Previous noncardiac vascular surgery	20 (8%)	14 (10%)	6 (6%)	0.25
Angiographic characteristics				
Coronary collaterals present (Rentrop grade ≥1)	91 (37%)	58 (41%)	33 (32%)	0.15
1-vessel coronary disease‡	143 (59%)	79 (56%)	64 (62%)	‡
2-vessel coronary disease	80 (33%)	46 (33%)	34 (33%)	0.75
3-vessel coronary disease	21 (9%)	16 (11%)	5 (5%)	0.08
Multivessel coronary disease	101 (41%)	62 (44%)	39 (38%)	0.34
Impaired left ventricular function§	90 (42%)	53 (42%)	37 (40%)	0.75

* Defined as total cholesterol >193 mg/dl (5 mmol/L) and/or low-density lipoprotein cholesterol >124 mg/dl (3.2 mmol/L), or on cholesterol-lowering medication.
† In 9 patients (7 cases, 2 noncases), Framingham CHD risk could not be calculated because of missing data.
‡ Reference category.
§ In 27 patients, the ventriculogram was not performed.
AP = angina pectoris; BMI = body mass index; CABG = coronary artery bypass grafting; MI = myocardial infarction; TIA = transient ischemic attack.

Table 2
Cardiovascular outcome and the presence and extent of coronary collateral circulation

First Cardiovascular Event After Index PTCA	Rentrop 0 (collaterals absent) (n = 153)	Rentrop 1 (not epicardial) (n = 13)	Rentrop 2 (partial epicardial) (n = 33)	Rentrop 3 (complete epicardial) (n = 45)	All Patients Studied (n = 244)
Cardiovascular death	—	—	1 (3%)	2 (4%)	3 (1%)
Sudden death	—	—	1 (3%)	1 (2%)	2 (1%)
Congestive heart failure	—	—	—	1 (2%)	1 (0.4%)
Nonfatal myocardial infarction	17 (11%)	5 (39%)	1 (3%)	3 (7%)	26 (11%)
Nonfatal stroke	1 (1%)	—	—	3 (7%)	4 (2%)
(Repeat) cardiovascular interventions	65 (43%)	5 (39%)	20 (61%)	18 (40%)	108 (44%)
Coronary artery bypass grafting	12 (8%)	—	6 (18%)	9 (20%)	27 (11%)
PTCA	47 (31%)	4 (31%)	11 (33%)	9 (20%)	71 (29%)
Percutaneous transluminal angioplasty (not coronary)	3 (2%)	1 (8%)	2 (6%)	—	6 (3%)
AAA surgery	1 (1%)	—	—	—	1 (0.4%)
Other vascular surgery	2 (1%)	—	1 (3%)	—	3 (1%)
Patients with events	83 (54%)	10 (77%)	22 (67%)	26 (58%)	141 (58%)

Data presented as number of patients with events (valid percent).
AAA = abdominal aortic aneurysm.

clear in relatively low-risk patients (HR 1.04, 95% CI 0.60 to 1.78).

The risk of subsequent cardiovascular events also tended to depend on the extent of coronary collateral circulation. Overall, Rentrop grade 1 coronary collaterals correlated with the greatest risk, particularly in relatively high-risk

Table 3
Risk of any first cardiovascular event in relation to presence and extent of coronary collateral circulation, unadjusted, adjusted, and stratified for Framingham coronary heart disease (CHD) risk at baseline (case-cohort study in 655 elective PTCA patients)

Coronary Collaterals	Low CHD Risk* (<13%) (59 cases; 50 noncases)	High CHD Risk* (≥13%) (75 cases; 51 noncases)	All Strata (141 cases; 103 noncases)	p Value (all strata)
Unadjusted				
Collateral presence (Rentrop ≥1)	0.96 (0.58–1.59)	2.23 (1.28–3.89)	1.41 (0.98–2.04)	0.07
Collateral extent (Rentrop 0 = reference)				
Rentrop 1	0.62 (0.13–2.93)	6.96 (2.73–17.8)	1.48 (0.35–6.22)	0.59
Rentrop 2/3	1.02 (0.60–1.72)	2.05 (1.16–3.61)	1.40 (0.97–2.02)	0.07
Adjusted†				
Collateral presence (Rentrop ≥1)	1.04 (0.60–1.78)	2.22 (1.08–4.55)	1.34 (0.91–1.98)	0.14
Collateral extent (Rentrop 0 = reference)				
Rentrop 1	0.78 (0.16–3.74)	8.07 (3.13–20.8)	1.91 (0.45–8.06)	0.38
Rentrop 2/3	1.08 (0.61–1.90)	1.78 (0.82–3.86)	1.27 (0.86–1.89)	0.23

Data presented as hazard ratio (robust 95% CI).
* In 9 patients (7 cases, 2 noncases) the Framingham CHD risk could not be calculated because of missing data.
† Adjusted for male gender, age, a history of myocardial infarction, a history of PTCA or CABG, and multivessel coronary disease.

patients (HR 8.07, 95% CI 3.13 to 20.8), but not in patients with a relatively low CHD risk (HR 0.78; 95% CI 0.16 to 3.74).

If the analyses were restricted to cardiac outcome alone, defined as a composite of cardiac death, nonfatal myocardial infarction, or any cardiac intervention (angioplasty or bypass) during follow-up, the results were essentially similar.

• • •

The results of the present study indicate that, overall, in patients with ischemic cardiac disease, the presence of coronary collaterals may represent a prognostic indicator of adverse cardiovascular outcome, especially if present to only a limited extent (Rentrop grade 1), rather than a favorable sign. However, in patients with relatively low cardiac risk, the presence of well-developed coronary collaterals may protect against subsequent cardiovascular or cardiac events. It is likely that in these relatively low-risk patients, the presence of well-developed collaterals marks sufficient collateral blood flow to adequately counterbalance the adverse effects of CHD.[12] However, particularly in relatively high-risk patients, the presence of barely developed coronary collaterals (Rentrop grade 1) may indicate such limited collateral function that it does not compensate for the disease severity, thus putting the patient at an even greater risk. In relatively high-risk patients, the presence of well-developed collaterals may also mark better myocardial perfusion, but the more adverse affects of ischemic heart disease tend to prevail. We, therefore, propose that the fate of a patient will ultimately be determined by the balance between the disease severity and the presence and extent of the coronary collaterals.

Acknowledgment: We gratefully acknowledge Koos J. Plomp, MD, cardiologist, Department of Cardiology, Heart Lung Center Utrecht, UMC Utrecht, Utrecht, The Netherlands, for scoring the 100 coronary angiograms to assess the interobserver variability of the collateral grading. We thank Michael Edlinger, MSc, for his accurate handling of the SMART data. We thank Daphne L. van der A, PhD, for her help in analyzing the case-cohort design. We thank Christine A.E. Broeders, MSc, for her excellent secretarial assistance.

Appendix

The SMART Study Group consisted of A. Algra, MD, PhD; Y. van der Graaf, MD, PhD; D.E. Grobbee, MD, PhD; G.E.H.M. Rutten, MD, PhD, Julius Center for Health Sciences and Primary Care; J.D. Banga, MD, PhD; F.L.J. Visseren, MD, PhD, Department of Internal Medicine; B.C. Eikelboom, MD, PhD; F.L. Moll, MD, PhD, Department of Vascular Surgery; L.J. Kappelle, MD, PhD, Department of Neurology; H.A. Koomans, MD, PhD, Department of Nephrology; W.P.T.M. Mali, MD, PhD, Department of Radiology; P.A.F.M. Doevendans, MD, PhD, and P.P.T. de Jaegere, MD, PhD, Department of Cardiology; all at University Medical Center Utrecht, Utrecht, The Netherlands.

1. Fujita M, Tambara K. Recent insights into human coronary collateral development. *Heart* 2004;90:246–250.
2. Seiler C. The human coronary collateral circulation. *Heart* 2003;89:1352–1357.
3. Koerselman J, van der Graaf Y, de Jaegere PP, Grobbee DE. Coronary collaterals: an important and underexposed aspect of coronary artery disease. *Circulation* 2003;107:2507–2511.
4. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. *Circulation* 1998;97:1837–1847.
5. Simons PC, Algra A, van de Laak MF, Grobbee DE, van der Graaf Y. Second manifestations of ARTerial disease (SMART) study: rationale and design. *Eur J Epidemiol* 1999;15:773–781.
6. Prentice RL. A case-cohort design for epidemiologic cohort studies and disease prevention trials. *Biometrika* 1986;73:1–11.
7. Rentrop KP, Cohen M, Blanke H, Phillips RA. Changes in collateral channel filling immediately after controlled coronary artery occlusion

by an angioplasty balloon in human subjects. *J Am Coll Cardiol* 1985;5:587–592.
8. Kurotobi T, Sato H, Kinjo K, Nakatani D, Mizuno H, Shimizu M, Imai K, Hirayama A, Kodama K, Hori M. Reduced collateral circulation to the infarct-related artery in elderly patients with acute myocardial infarction. *J Am Coll Cardiol* 2004;44:28–34.
9. Rentrop KP, Thornton JC, Feit F, Van Buskirk M. Determinants and protective potential of coronary arterial collaterals as assessed by an angioplasty model. *Am J Cardiol* 1988;61:677–684.
10. van Liebergen RA, Piek JJ, Koch KT, de Winter RJ, Schotborgh CE, Lie KI. Quantification of collateral flow in humans: a comparison of angiographic, electrocardiographic and hemodynamic variables. *J Am Coll Cardiol* 1999;33:670–677.
11. Barlow WE, Ichikawa L, Rosner D, Izumi S. Analysis of case-cohort designs. *J Clin Epidemiol* 1999;52:1165–1172.
12. Werner GS, Ferrari M, Heinke S, Kuethe F, Surber R, Richartz BM, Figulla HR. Angiographic assessment of collateral connections in comparison with invasively determined collateral function in chronic coronary occlusions. *Circulation* 2003;107: 1972–1977.